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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,629	08/05/2003	Ayoub Rashtchian	60126-002US	6375

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EXAMINER
POPA, ILEANA

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,629	RASHTCHIAN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-18 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-18 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 01/31/2007 has been entered.

2. Claims 5, 6, 19, and 20 have been cancelled. Claims 22 and 23 are new.

Claims 1-4, 7-18, and 21-23 are pending and under examination.

35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 11, 12, 22, and 23 are rejected under 35 USC § 102(b) as being anticipated by Stemmer et al. (U.S. Patent No. 5,834,252, of record), as evidenced by Maa et al. (Biotechnology and Bioengineering, 1997, 54: 503-512) and Takahashi et al. (Sci SRKE, 2000, 56: pl1) for the reasons of record set forth in e prior Office actions.

Applicant argues that (i) there is no art of record that states that polymerases are inactivated by foaming and therefore, the Examiner's statement regarding the motivation to add antifoam to PCR reaction to prevent protein inactivation is not appropriate, and (ii) Stemmer is not an enabling reference because, since the reference fails to describe either the identity or the concentration of any suitable antifoam agents for use in PCR, there is no teaching that would have taught one of skill in the art how to make and use an antifoam reagent in a PCR reaction. In support of this assertion, Applicant submits a Declaration under 37 C.F.R. § 1.132 by Mr. Berninger, a researcher skilled in the molecular biology art. Mr. Berninger states that the single instance in which Stemmer discloses antifoam agents is in the context of physiological conditions suitable for PCR (column 30, lines 7-30). Since PCR conditions are well outside the range compatible with cell viability, Mr. Berninger asserts that the teachings of Stemmer are deficient with respect to the PCR conditions and not instructive so as to enable one of skill in the art to practice PCR as it is generally performed in the field and that he would never use the general direction as to antifoam agents offered in Stemmer et al. and would not allow those under his direction to use the protocol of Stemmer. Mr. Berninger further states that the teachings of Stemmer would have not enabled one of skill in the art to select and use an appropriate antifoam reagent without undue experimentation, and therefore, the reference is not enabling. Applicant argues that Examiner's assertion that, since the claims do not specify particular antifoams or concentrations, the failure of Stemmer to identify a suitable antifoam and suitable

concentrations is irrelevant is not appropriate because one of skill in the art does not look at the claims, but at the specification to find out how to practice the claimed invention (MPEP 2164.08). Applicant argues that the instant specification fully describes antifoams agents and concentrations whereas Stemmer provides none. In addition to their arguments, Applicant provides a new IDS citing two new references: Foxall et al. (U.S. Patent No. 5,985,569) and Durmowicz et al. (U.S. Patent No. 5,962,273). With respect to Foxall et al., Mr. Berninger states that the reference teaches the use of antifoam in single strand displacement amplification (SDA), but does not specify the type of antifoam used, does not teach how to select an appropriate antifoam agent, and does not offer any explanation for the inclusion of an antifoam agent. Mr. Berninger points out to Example 10, wherein different conditions are tested for optimum results and wherein optimum results are obtained when the antifoam agent is not present and concludes that one of skill in the art would not be led to use antifoam in SDA. With respect to Durmowicz et al., Mr. Berninger states that the reference teaches SDA and not PCR, wherein the reaction conditions for SDA are different from those of PCR. Although Durmowicz et al. disclose the use of 0.015% antifoam, the type of antifoam is not disclosed. Mr. Berninger indicates that it is recognized in the field that many different antifoam agents are commercially available and therefore, a general instruction to use 0.015% antifoam is not descriptive enough for even a practitioner with substantial experience in the field of nucleic acid amplification. For this reason, one of kill in the art would have to laboriously test essentially all antifoams and combinations thereof at a range of concentrations

around 0.015% in order to identify a suitable antifoam agent. For all the reasons above, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

First, it is noted that the prior art teaches: (i) that proteins in general and Taq polymerase in particular are inactivated by foam and (ii) the use of antifoam agents to prevent denaturation of proteins by foaming (see Maa et al., Abstract, p. 503, columns 1 and 2, p. 511, column 2, last paragraph; Takahashi et al., p. 10, *Lack of a PCR Product in the Whole-Cell Extracts Samples*). Second, with respect to the argument that the paragraph in Stemmer et al. does not identify a suitable antifoam and concentration to be used in PCR, it is noted that the rejected claims are broadly drawn to any antifoam agents and no concentration is mentioned. Applicant's argument that one of skill in the art does not look at the claims but at the specification to find out how to practice the claimed invention is not found persuasive because, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. It is noted that MPEP 2164.08 cited by the Applicant deals with enablement and not art rejection, wherein for enablement one would look at the specification for guidance of how to make and use the invention. Among the factors to be considered under enablement are the breadth of the claims and determination of whether one of skill in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation. In the instant case, although the claims are broadly drawn to any antifoam agent with no particular

concentration disclosed, choosing the right antifoam agent and the appropriate concentration is nothing but optimization that can be achieved by routine experimentation. Because optimization can be achieved by routine experimentation, Mr. Berninger's statement that one of skill in the art would have to laboriously test essentially all antifoams and combinations thereof at a range of concentrations in order to identify suitable antifoams.is also not found persuasive. One of skill in the art would have known that PCR machines could be used in a high throughput format and thus, one of skill in the art would have identified the right conditions by using just routine experimentation. The argument that Stemmer only discloses antifoam agents in the context of physiological conditions suitable for PCR is not found persuasive. The level of skill in the art is such that one of skill in the art would readily recognize suitable PCR conditions, especially that conditions for PCR were well known in the prior art. For example, one of skill in the art would have known to use the suitable buffers for DNA polymerase, wherein the suitable buffers do not contain undesirable reagents such as chelators, this was common knowledge in the art before the invention was made. On the other hand, one of skill in the art would have readily recognized the utility of using antifoam agents in PCR (it is noted that PCR uses detergents), especially that the art teaches that proteins in general could be inactivated by foaming, that antifoam agents could be used to prevent protein degradation by foaming, and that antifoam agents could be used in nucleic acid amplification reactions such as SDA. Applicant's argument that SDA and PCR are very different and that the teachings of Foxall et al. or

Durmowicz et al. give no guidance or expectation that any antifoam agent would be compatible with PCR is just an argument that is not supported by any evidence. The fact that SDA and PCR are different amplification procedures is irrelevant because they both use DNA polymerases and it is the polymerase activity that needs to be preserved. Additionally, Mr. Berninger's argument that the prior art does not offer an explanation for the inclusion of an antifoam agent is not found persuasive, because, based on what was known in the prior art, one of skill in the art would have known that such agents are useful to prevent polymerase degradation by foaming (see above). Therefore, one of skill in the art would have known to use antifoam agents to improve PCR efficiency by reducing enzyme degradation, especially that the prior art teaches the use of antifoam agents in nucleic acid amplification reactions (see Foxall et al. and Durmowicz et al. in SDA; Stemmer et al. in PCR).

For these reasons the claimed invention is anticipated by Stemmer et al.

35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 7, 11, 15-18, and 21-23 are rejected under 35 USC § 103(a) as being unpatentable over Blaschke et al. (J Immunol Methods, 2000, 246: 79-

90, of record), in view of each Stemmer taken with Maa et al. and Takahashi et al., Varadaraj et al. (Gene, 1994, 140:1-5, Abstract, of record), and Swedlow et al. (Anal Chem, 1997, 69: 848-855) for the reasons of record set forth in e prior Office actions.

Applicant argues that Varadaraj et al. teach that ethanol inhibits PCR amplification, and since the Examiner stated, in the non-final Office action, that ethanol is an antifoam, the conclusion is that some antifoams are deleterious to PCR and therefore, Varadaraj et al. teach away from the instant invention and confirms the surprising nature of the results obtained by the Applicant that certain antifoams at particular concentrations can be used in PCR without substantially inhibiting the reaction. Applicant argues that it is improper to combine references that teach away from their combination (MPEP 2145). Applicant continues arguing that Swerdlow et al. do not mention that a detergent was the source of bubbles and that the bubbles could have been generated after the PCR reaction during the liquid flow to the chromatographic column and therefore, there have been no motivation to add antifoam to the PCR reagent. Applicant argues that Swerdlow et al. did no use an antifoam and that nothing in any of the cited references teaches or suggest that antifoam would be useful to remove the type of bubbles described by Swerdlow et al. With respect to Blaschke et al., Applicant argues that, since they obtain single band products, one of skill in the art would have no motivation to modify the their teachings, as suggested by the Examiner. With respect to Stemmer, Applicant argues that the reference

is not enabling for the reasons above. Therefore, Applicant concludes that there is nothing in the cited combination of references that would motivate one of skill in the art to use an antifoam agent in PCR and the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

It is noted that the art teaches that ethanol is an antifoam agent and also that ethanol inhibits Taq polymerase. However, with the exception of ethanol, the art does not teach that antifoam agents in general inhibit Taq polymerase. On the contrary, the art teaches the use of such agents in nucleic acid amplification procedures such as SDA and PCR (see above). The teachings of Varadaraj et al. are therefore consistent with what was known in the prior art (i.e., that ethanol is inhibitory in PCR). There is no teaching in Varadaraj et al. that other antifoam agents inhibit PCR. Based on these teachings, one of skill in the art would not consider Varadaraj et al. as teaching away from the instant invention and would know not to use ethanol in PCR. On the other hand, one of skill in the art would know that other antifoam agents could be used in PCR.

With respect to Swerdlow et al., the fact that they do not mention that a detergent was the source of bubbles, wherein the bubbles could have been generated after the PCR reaction is irrelevant. Swerdlow et al. was used not because they teach antifoam agents, but because they teach the necessity to eliminate the air bubbles before fluorescent detection to improve the sensitivity of the reaction (Abstract, p. 850, column 1, Fig., p. 855, column 2). Therefore, although they teach eliminating bubbles by using a chromatography column and not an

antifoam agent, Swerdlow et al. do teach the necessity of removing air bubbles before fluorescence detection to improve signal-to-noise ratios (p. 855, column 2). Based on these teachings, one of skill in the art would have realized the importance of eliminating air bubbles before the fluorescent detection of amplified products would have known to use antifoam agent as an easier alternative to a chromatography column, because Stemmer et al. teach their use in PCR (see above). Applicant's argument that, since Blaschke et al. teach obtaining single bands, one of skill in the art would not have been motivated to modify their method by adding the detergents of Varadarj et al. is not found persuasive. Blaschke et al. teach obtaining single bands for DNAs encoding for cytokines, wherein these DNAs do not have a high GC content. However, their method is applicable to any DNA, regardless of the GC content. Since Varadaraj et al. clearly teach that addition of detergents improves the specificity of the amplified products, especially when one deals with G+C-rich DNAs, one of skill in the art would have known to improve specificity for the method of Blaschke et al. by using the detergents of Varadaraj et al., especially when amplifying G+C-rich DNAs. Applicant's argument that Stemmer et al. is not enabling is not found persuasive for the reasons stated above. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 1, 9, 11-13, 22, and 23 are rejected under 35 USC § 103(a) as being unpatentable over Stemmer et al. taken with Maa et al. and Takahashi et

al., in further view of Kyle (U.S. Patent No. 5,658,787, of record) for the reasons of record set forth in the prior Office actions.

Applicant submits that the deficiencies of Stemmer et al., as described above, are not cured by Kyle because there is nothing in Kyle that would have provided one of skill in the art a reasonable expectation of success in using any antifoam agent, let alone 1520-US, in PCR. Since no *prima facie* case of obviousness was established, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the reasons stated above for the rejection under 102(b), since the disclosure of Stemmer et al. is enabling. Beside an argument, Applicant did not provide any evidence as to why 1520-US could not be successfully used in PCR. For these reasons and for the reasons set forth in the prior Office actions, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 1, 8-14, 22, and 23 are rejected under 35 USC § 103(a) as being unpatentable over Stemmer et al. taken with Maa et al., Takahashi et al., and Kyle, in further view of Sigma catalog (1998, of record) and Wieranga (U.S. Patent No. 5,968,889, of record) for the reasons of record set forth in the prior Office actions.

Applicant submits that the deficiencies of Stemmer et al. and Kyle, as set forth above, are not cured by either the Sigma catalog or Wieranga because neither teaches or suggests that antifoam agents might be useful in a PCR reaction, nor does the Sigma catalog teach or suggest that combinations of

antifoam agents would be useful in PCR. Since no *prima facie* case of obviousness was established, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the reasons stated above for the rejection under 102(b), since the disclosure of Stemmer et al. is enabling. Beside an argument, Applicant did not provide any evidence as to why combinations of antifoam agents could not be successfully used in PCR. Sigma catalog was cited for teaching that anti-foaming agents can be supplied as a mixture of organic anti-foams and silicone-based anti-foams, and that O-30 is an organic antifoaming agent and Wieranga was cited for teaching synergism between silicone-based (i.e., 1520-US) and organic antifoam agents. While neither Sigma catalog nor Wieranga teach using these combinations in PCR, one of skill in the art would have been motivated to look for antifoam agents known in the art because the art teaches that antifoam agents in general could be used in nucleic acid amplification reactions. By doing this, one of skill in the art would also have necessarily identified both Wieranga and the Sigma catalog both teaching combinations of silicone-based (i.e., 1520-US) and organic antifoamers, wherein such combinations act synergistically. For these reasons and for the reasons set forth in the prior Office actions, the claimed invention was *prima facie* obvious at the time the invention was made.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD